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Rhodium-Catalyzed Asymmetric Hydrogenation of β-Branched Enamides for the Synthesis of β-Stereogenic Amines

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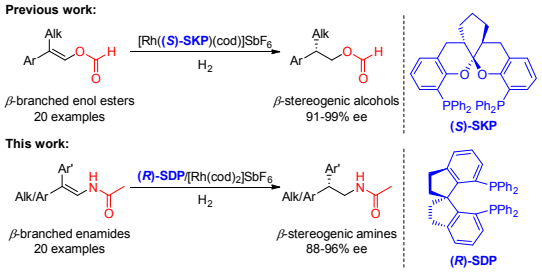
Using a rhodium complex of a bisphosphine ligand (*R*)-SDP, β-branched simple enamides with a (*Z*)-configuration were hydrogenated to β-stereogenic amines in quantitative yields and with excellent enantioselectivities (88-96% ee).

Chiral amines are undoubtedly some of the most common structural units present in natural products, chiral drugs and chiral catalysts, making the preparation of such compounds containing the chiral amine structural motif very attractive in the field of asymmetric catalytic synthesis. While dozens of methods have been developed for the construction of α-stereogenic amines, synthetic methodologies for the preparation of β-stereogenic amines are relatively few, even though they can be used in many applications.[1] The main methodologies for the synthesis of such compounds include acylative kinetic resolution of racemic β-branched amines,[2] asymmetric hydroaminomethylation of terminal monosubstituted alkenes,[3] enantioselective addition of amines to terminal disubstituted alkenes,[4] asymmetric conjugate addition of nucleophiles to nitroalkenes,[5] and asymmetric reduction of unsaturated nitrogen-containing substrates.[6-9] Among them, the asymmetric hydrogenation (AH, asymmetric reduction with hydrogen gas) is the most practical methodology due to its high efficiency and environmental friendliness.[10] Until now, only three types of substrates have been reported for the hydrogenative synthesis of β-stereogenic amines. One route involves the AH of β-branched nitroalkenes, followed by reduction of the nitro functionality to an amino group.[7] High enantioselectivities were obtained for substrates bearing a β-acyl, methyl, or ethyl substituent. A second route involves the AH of β-branched allylic amines or amides to give products possessing at least one β-primary alkyl substituent.[8] The third route involves the AH of β-branched enamines. However, only the hydrogenation of β-branched dehydroamino acids and esters has been reported;[9] no AH of β-branched simple enamines has been studied, probably due to difficulties related to the stereocontrol of the reaction. This methodology would provide an alternative hydrogenative route for the synthesis of the above-mentioned β-aryl-β-alkyl-substituted chiral amines, and even β,β-diaryl-substituted chiral amines which have not been previously reported.

Continuing our efforts concerning AH,[11] we have recently developed an efficient Rh-catalyzed AH of β-branched enol esters. Using a bisphosphine ligand bearing a large bite angle and enol ester substrates possessing an *O*-acyl directing group, the β-stereogenic alcohols were obtained in quantitative yields and with excellent enantioselectivities (Scheme 1).[11i] In consideration of the fact that the catalytic mechanism and stereocontrol for the Rh-catalyzed AH of enamides is very similar to that of enol esters, we envisage that β-stereogenic amines can be synthesized via a Rh-catalyzed AH by using β-branched enamide substrates possessing an *N*-acyl directing group and bisphosphine ligands bearing a large bite angle. As far as we know, simple enamides bearing α-branched aryl and alkyl substituents are model substrates widely utilized in Rh-catalyzed AH,[12] but simple enamides bearing only β-branched aryl and alkyl substituents are a new type of substrate which have not been studied for AH (Figure 1, NHAc is taken as an example for the amido group).



Scheme 1 The Asymmetric Hydrogenation of β-Branched Enol Esters and Enamides.

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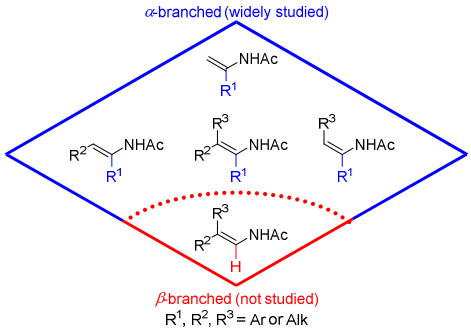
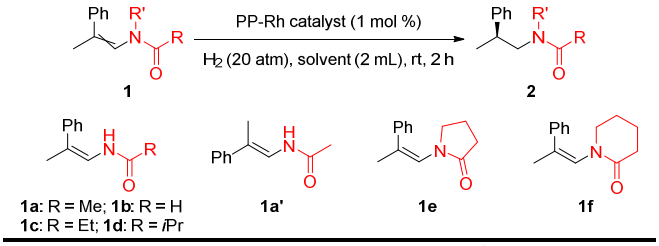


Figure 1 Simple Enamides for Asymmetric Hydrogenation.

The initial hydrogenation reactions were conducted on the two isomers of *N*-(2-phenylprop-1-en-1-yl)acetamide, which were easily synthesized from 2-phenylpropanal and acetamide. Both of them were reduced completely in 2 hours with the (*Z*)-isomer **1a** giving better enantioselectivity than the (*E*)-isomer **1a'** (Table 1, entries 1 and 2). Different bisphosphine ligands were then tested in the Rh-catalyzed hydrogenation of **1a**. Similar to the trend observed for the AH of *β*-branched enol esters,[11i] ligands bearing a large bite angle showed higher activities (entries 1, 3-5 vs 6-8). The catalytic system (*R*)-SDP/$[Rh(cod)_2]SbF_6$ gave the best results, providing the desired product in 99% conversion and 93% ee (entry 1).[13] After screening of different solvents, the enantioselectivity could be further increased to 96% ee by using ether solvents, especially THF (entries 9-14). When the hydrogenation is carried out at lower hydrogen pressures, the enantioselectivity is maintained, but prolonged reaction times are required for complete conversion (entries 15 and 16). Other amido groups have also been investigated but did not improve the enantioselectivity (entries 17-21).

With the optimized reaction conditions in hand, we investigated the substrate scope (Scheme 2). All the reduced products, regardless of the electronic properties of R^1 and the steric hindrance of R^2, were obtained in excellent yields and enantioselectivities. The electron-withdrawing 4-halogen-substituted amides **2g-i** were obtained in 90%, 96%, and 96% ee's, respectively. The 4-Ph-substituted amide **2j** gave relatively lower ee (91%), while the 4-CF_3-substituted amide **2k** gave better ee (96%). For substrates bearing an electron-donating group, such as a methyl substituent at the 4-, 3-, and 2-positions, the desired products **2l-n** were obtained in 93%, 96%, and 96% ee's, respectively. Increasing the size of the 4-alkyl group from Me to Et, *i*Pr, and *t*Bu showed a slight effect on enantioselectivity (**2o-q**). A substrate possessing the electron-donating 4-OMe group gave its related product **2r** with 94% ee. Disubstituted substrates bearing 1,3-benzodioxol-5-yl, 1-naphthyl, or 2-naphthyl groups gave comparatively lower enantioselectivities (**2s-u**). Additionally, substrates bearing different R^2 substituents have also been tested. The use of larger alkyl substituents led to a decrease in enantioselctivity (**2v-x**). A substrate bearing *β*-2-naphthyl and *β*-phenyl groups was also subjected to hydrogenation to give the desired product **2y** with 96% ee. This is the first time that *β*,*β*-diayl-substituted *β*-stereogenic amines have been obtained via AH.

Table 1 Condition Optimization.



entry[a]	sub.	cat.	sol.	conv (%)[b]	ee (%)[c]
1	**1a**	**A**	DCM	99	93
2	**1a'**	**A**	DCM	99	-76
3	**1a**	**B**	DCM	99	58
4	**1a**	**C**	DCM	99	-60
5	**1a**	**D**	DCM	99	-18
6	**1a**	**E**	DCM	65	12
7	**1a**	**F**	DCM	85	-80
8[d]	**1a**	**G**	DCM	0	/
9	**1a**	**A**	MeOH	99	86
10	**1a**	**A**	toluene	99	88
11	**1a**	**A**	EtOAc	99	92
12	**1a**	**A**	THF	99	96
13	**1a**	**A**	dioxane	99	94
14	**1a**	**A**	DME	99	94
15[e]	**1a**	**A**	THF	99	96
16[f]	**1a**	**A**	THF	99	96
17	**1b**	**A**	THF	99	30
18	**1c**	**A**	THF	99	60
19	**1d**	**A**	THF	60	nd
20	**1e**	**A**	THF	99	91
21	**1f**	**A**	THF	99	39

[a] Conditions: **1** (0.2 mmol), catalyst (1 mol %), H_2 (20 atm), solvent (2 mL), 25 °C, 2 h, unless otherwise noted. Please see the structures in the Supporting Information for **A**: (*R*)-SDP/$[Rh(cod)_2]SbF_6$, **B**: $[Rh((R)\text{-PhanePhos})(cod)]BF_4$, **C**: $[Rh((R,R)\text{-Me-FcPhos})(cod)]BF_4$, **D**: (*R*)-BINAP/$[Rh(cod)_2]SbF_6$, **E**: (*R*,*Sp*)-JosiPhos/$[Rh(cod)_2]SbF_6$, **F**: $[Rh((R,R)\text{-BenzP*})(nbd)]SbF_6$, and **G**: (*R*,*R*)-Me-DuPhos/$[Rh(cod)_2]SbF_6$. [b] The conversions were calculated from ^1H NMR spectra. [c] The ee's were determined by HPLC using chiral columns. [d] Repeated result. [e] 10 atm, 8 h (61% conversion was obtained after 2 h) . [f] 5 atm, 24 h (49% conversion was obtained after 8 h).

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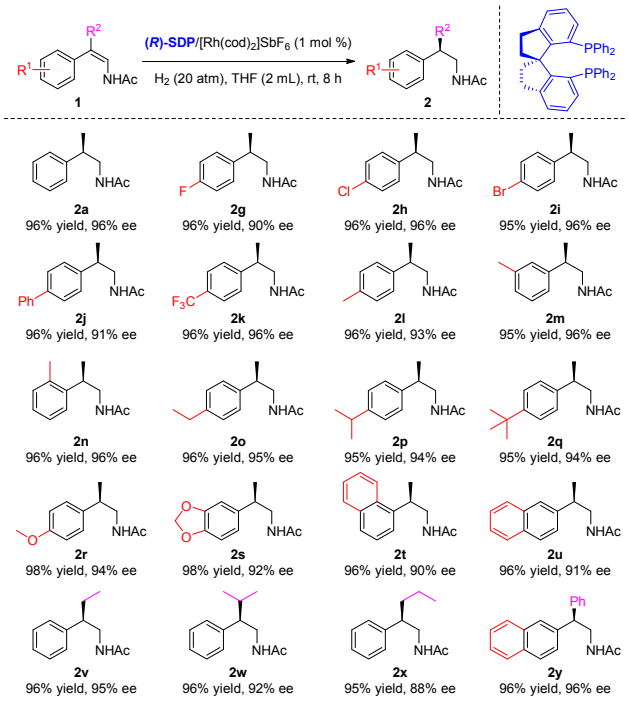
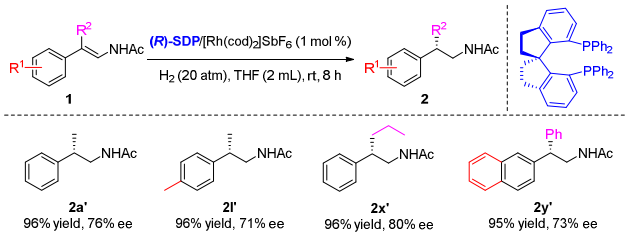


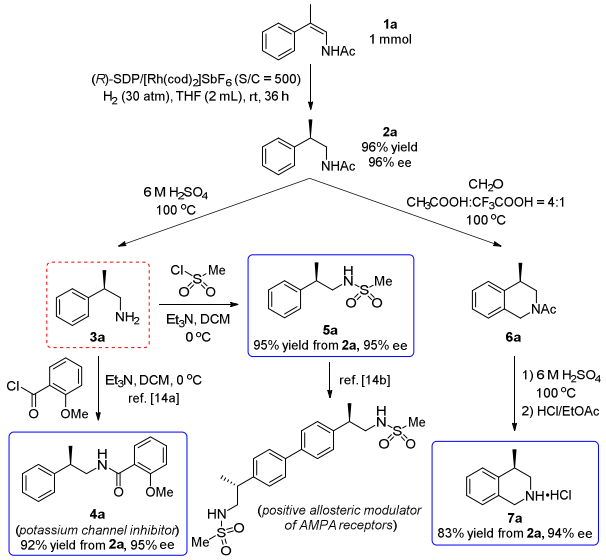
Scheme 2 Substrate Scope.

Some of the (*E*)-isomers have also been evaluated under the optimized conditions (Scheme 3). All the substrates **2a'**, **2l'**, **2x'**, and **2y'** were hydrogenated to obtain the corresponding products in complete conversions. However, comparitively lower enantioselectivities (71-80% ee) were observed compared with the (*Z*)-isomers (88-96% ee).



Scheme 3 Asymmetric Hydrogenation of (*E*)-Isomers.

To demonstrate the applicability of this methodology, the hydrogenation was conducted at a higher S/C and the product was transformed to useful bioactive molecules (Scheme 4). For instance, hydrogenation of **1a** at 500 S/C, under 30 atm hydrogen pressure, and for 36 h produced the *β*-stereogenic amide **2a** in 96% yield and with 96% ee. The amide **2a** was smoothly hydrolyzed to the corresponding *β*-stereogenic amine **3a**, which can be further derivatized to a potassium channel inhibitor **4a** in high yield with no loss in enantioselectivity.[14a] This *β*-stereogenic amine **3a** can also reacted with methylsulfonyl chloride to give a sulfamide **5a**, which is a key intermediate for the preparation of a positive allosteric modulator of AMPA receptors.[14b] After cyclization with paraformaldehyde in an acidic medium followed by hydrolyzation, the amide **2a** was simply converted to chiral 4-methyl-1,2,3,4-tetrahydroisoquinoline **7a**, which is a useful synthon for the preparation of several bioactive compounds.[15]



Scheme 4 Applications for the Synthesis of Bioactive Compounds.

In conclusion, using the bisphosphine ligand (*R*)-SDP bearing a large bite angle, *β*-branched simple enamides with a (*Z*)-configuration were enantioselectively hydrogenated for the first time to give the corresponding products in quantitative yields and with excellent enantioselectivities. Furthermore, this methodology can be applied to the preparation of several bioactive compounds bearing the important *β*-stereogenic amine skeletons.

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β-Branched simple enamides were hydrogenated to give *β*-stereogenic amines in quantitative yields and with excellent enantioselectivities.